

Armed Killers Face Off against Cytomegalovirus

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Despite significant progress in prevention and treatment of cytomegalovirus (CMV) infection in allogeneic hematopoietic cell transplant (HCT) recipients, CMV reactivation occurs in approximately 60% to 70% of seropositive allogeneic HCT recipients and remains a risk factor for transplantation-related morbidity and mortality. Over the years, the incidence of CMV disease in HCT recipients has declined dramatically as a result of efforts to prevent primary infection in seronegative patients and use of prophylactic or pre-emptive antiviral therapy in seropositive patients. However, current antiviral therapy is associated with significant toxicity. Even though CMV disease is rare today, CMV seropositivity is associated with inferior survival in various subsets of patients, especially in recipients of T cell depleted grafts [1]. It has been suggested that CMV exerts immunomodulatory effects in yet unclear ways, indirectly influencing graft-versus-host disease (GVHD) and bacterial and fungal infections. Clearly, novel approaches to reduce CMV-associated morbidity and mortality in HSCT recipients are needed. Several new approaches are being evaluated: new and less toxic antiviral drugs, vaccines, and immune cellular therapies.

In this issue of BBMT, Lum et al. [2] describe pre-clinical studies of a novel cellular approach against CMV infection, which they hope to test as adoptive immunotherapy in the future. They have developed ex vivo expanded activated cytotoxic T cells (ATC) armed by bispecific polyclonal anti-CD3 \times anti-CMV Abs (CMVBi). The idea of adoptive immunotherapy with cytotoxic T lymphocytes to control viral replication is not new. Decades ago, it was found that natural killer (NK) and cytotoxic T cell mediated cellular immunity is crucial in suppressing CMV replication and preventing CMV disease after HCT [3,4]. Riddell et al. [5] have demonstrated that adoptive transfer of cytotoxic CD8⁺ T cells from the donors into hematopoietic stem cell transplantation (HSCT) re-

cipients who were at risk for CMV protected them from CMV-related complications, but adequate numbers of CMV-specific CD4⁺ cells were important for persistence of CMV immunity.

Lum et al. [2] demonstrate that the ex vivo expanded ATC armed by CMVBi have potent anti-CMV specific cytotoxicity against CMV infected fibroblasts while sparing uninfected cellular targets. They further demonstrate that the effect was not due to Ab-dependent cell-mediated cytotoxicity or complement-mediated cytotoxicity, was not restricted by need for HLA compatibility with infected target cells, was not affected by irradiation, and did not seem to induce substantial alloreactive responses to HLA disparate targets. It is important to mention that CMVBi armed with ATC were highly active at effector:target ratio of as low as 1:1, suggesting that low numbers of ATC might be sufficient to elicit an effective anti-CMV activity, which could minimize side effects associated with infusion of alloreactive cytotoxic cells in high amounts.

There are several potential strengths and limitations for this approach. One strength is the use of polyclonal Abs targeting multiple CMV epitopes increases the chance that the multiple CMV genotypes will be susceptible and reduces the well known ability of CMV to evade cellular immune responses. One concern is that the CMVBi was constructed by using Cytogam (CSL Behring, King of Prussia, PA), a polyclonal human immunoglobulin preparation, which contains multiple non-CMV directed Abs mixed among the CMV Abs. It raises the theoretical concern that a significant fraction of armed bispecific Abs could result in unpredictable autoimmune responses. In addition, Cytogam preparation is subject to significant variability from batch to batch, which could be associated with variable efficacy and toxicity.

Notwithstanding, this approach seems quite promising. The authors suggest that lower costs, possibly less toxicity, and the lack of need of HLA matching with the recipient are potential advantages over other antiviral engineered Ab and other T cell adoptive immunotherapy approaches. However, these will need to stand the rigors of clinical studies to know if these hopes are realized. Such studies will need to establish dose, dose schedule, and durability of CMV protection. In addition to CMV disease protection, such studies will need to demonstrate safety without an unintended increase in GVHD or development of autoimmune sequelae.

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There are other adoptive cellular approaches that also seem promising. Because NK-cell mediated antiviral response plays a significant role in CMV clearance [6], expansion of "CMV-armed NK-cells" could be considered for adoptive immunotherapy which, like the Lum approach, could minimize the risk of GVHD. Other competing strategies are also being evaluated. A DNA vaccine ASP0113 (TransVax) against CMV has already undergone testing in phase 1 and 2 studies and was shown to be safe, immunogenic, and effective with impressive reduction in the CMV viremia episodes 1 year after transplantation in CMV seropositive HCT recipients as compared to placebo. The vaccine was well-tolerated and the incidence of common adverse events after HCT including GVHD or secondary infections was not significantly increased [7]. A phase 3 study will be initiated in the near future. There is also progress in drug therapy for CMV infection in HSCT recipients as well. A new orally bioavailable lipid conjugate of cidofovir (CMX001) is currently being investigated for the prevention and treatment of double-stranded DNA viruses, including CMV. A recently completed randomized phase 2 trial confirmed acceptable safety, tolerability, and antiviral activity of CMX001 in CMV seropositive HSCT recipients [8]. To be adopted in the clinic, CMVBi will need to show comparable or better efficacy and safety compared with these strategies.

In conclusion, Lum et al. [2] present intriguing preclinical data utilizing CMVBi armed with ATC against CMV infected fibroblasts. Results described by the authors clearly warrant further investigation, but feasibility of this approach needs to be confirmed in phase 1 and 2 studies.

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